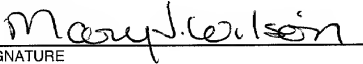


FORM PTO-1390 (REV 11-98)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER <b>2051-36</b>
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) <b>09/J 85598</b> <small>Uskobyh</small>
INTERNATIONAL APPLICATION NO. <b>PCT/CA98/00773</b>	INTERNATIONAL FILING DATE <b>7 August 1998</b>	PRIORITY DATE CLAIMED <b>15 August 1997</b>
TITLE OF INVENTION <b>PHARMACEUTICAL COMPOSITIONS COMPRISING CEFUROXIME AXETIL</b>		
APPLICANT(S) FOR DO/EO/US <b>SHERMAN</b>		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19 <sup>th</sup> month from the earliest claimed priority date. 5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)). a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has <b>NOT</b> expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). <b>Items 11. To 16. Below concern document(s) or information included:</b> 11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input checked="" type="checkbox"/> Other items or information.      Copy of International Search Report		

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) <b>09/485598</b> (invention)	INTERNATIONAL APPLICATION NO. <b>PCT/CA98/00773</b>	ATTORNEY'S DOCKET NUMBER <b>2051-36</b>
17. <input checked="" type="checkbox"/> The following fees are submitted:		<b>CALCULATIONS</b> PTO USE ONLY
<b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</b> -- Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....\$970.00 -- International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO .....\$840.00 -- International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$760.00 -- International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) .....\$670.00 -- International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) .....\$96.00		
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		
		\$ 840.00
		\$ 0.00
CLAIMS	NUMBER FILED	NUMBER EXTRA
Total Claims	14	-20 = 0
Independent Claims	1	-3 = 0
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)		+\$260.00
<b>TOTAL OF ABOVE CALCULATIONS =</b>		<b>\$ 840.00</b>
Reduction by 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).		
<b>SUBTOTAL =</b>		<b>\$ 840.00</b>
Processing fee of \$130.00, for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		
		\$ 0.00
<b>TOTAL NATIONAL FEE =</b>		<b>\$ 840.00</b>
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property		\$ 0.00
Fee for Petition to Revive Unintentionally Abandoned Application (\$1,210 - Small Entity Fee = \$605)		\$ 0.00
<b>TOTAL FEES ENCLOSED =</b>		<b>\$ 840.00</b>
		Amount to be: refunded \$ charged \$
a. <input checked="" type="checkbox"/> A check in the amount of \$840.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 14-1140 in the amount of \$_____ to cover the above fees. A duplicate copy of this form is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.		
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>		
<b>SEND ALL CORRESPONDENCE TO:</b>		
 SIGNATURE		
NIXON & VANDERHYE P.C. 1100 North Glebe Road, 8 <sup>th</sup> Floor Arlington, Virginia 22201 Telephone: (703) 816-4000		
Mary J. Wilson NAME		
<b>32,955</b> REGISTRATION NUMBER		<b>February 14, 2000</b> Date

09/485598

426 Rec'd PCT/PTO 14 FEB 2000

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

**SHERMAN**

Atty. Ref.: **2051-36**

U.S.. National Phase of PCT/CA98/00773

Group: **Unknown**

(Filed: August 7, 1998)

Filed: **February 14, 2000**

Examiner: **Unknown**

For: **PHARMACEUTICAL COMPOSITIONS COMPRISING  
CEFUROXIME AXETIL**

\* \* \* \* \*

**February 14, 2000**

Assistant Commissioner for Patents  
Washington, DC 20231

Sir:

**PRELIMINARY AMENDMENT**

Prior to calculation of the filing fee and in order to place the above identified application in better condition for examination, please amend the claims as follows:

**IN THE CLAIMS**

Claim 5, line 1, change "any of claims 1 to 4" to --claim 1--.

Claim 6, line 1, change "any of claims 1 to 5" to --claim 1--.

Claim 9, lines 1 and 2, change "any of claims 1 to 5" to --claim 1--.

**SHERMAN**

U.S. National Phase of PCT/CA98/00773

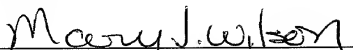
**REMARKS**

The above amendments are made to place the claims in a more traditional format.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By:



**Mary J. Wilson**

Reg. No. 32,955

**MJW:kd**

1100 North Glebe Road, 8th Floor  
Arlington, VA 22201-4714  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100

PHARMACEUTICAL COMPOSITIONS COMPRISING  
CEFUROXIME AXETIL

BACKGROUND

5 Cefuroxime axetil is an antibiotic effective against a wide spectrum of microorganisms. Antibiotics for oral administration should be in a form which provides high bioavailability, whereby absorption into the bloodstream from the gastro-intestinal tract is maximized.

10 For cefuroxime axetil, the prior art discloses substantial difficulties in making compositions for oral administration providing high bioavailability.

Pure cefuroxime axetil can be produced in crystalline form or amorphous form.

15 U.S. patent 4820833 discloses that the pure amorphous form is more soluble in water than the pure crystalline form and gives higher bioavailability upon oral administration.

20 U.S. patent 4897270 further discloses that film coated tablets comprising cefuroxime axetil (even in amorphous form) give low levels of absorption into the blood stream unless the tablets are formulated such that, when the tablet is ingested, the film coating ruptures very rapidly and the core then disintegrates immediately.

25 The prior art thus teaches that good absorption from tablets comprising cefuroxime axetil can be achieved only if the cefuroxime axetil used in the formulation is in pure amorphous form and the tablets contain sufficient disintegrant to cause them to disintegrate immediately in gastro-intestinal fluid.

30 It is the object of the present invention to overcome these limitations disclosed in the prior art.

More specifically, one object of the present invention is to enable compositions of cefuroxime axetil for oral administration exhibiting high bioavailability without requiring use of cefuroxime axetil in pure amorphous form; and a second object of the present invention is to enable tablets for oral administration exhibiting high bioavailability without requiring that the tablets disintegrate immediately in gastro-intestinal fluid.

#### BRIEF SUMMARY OF THE INVENTION

It has been found that the water solubility and hence bioavailability of cefuroxime axetil can be enhanced by making a co-precipitate comprising cefuroxime axetil and a water-soluble excipient.

It has further been found that tablets made from the co-precipitate exhibit satisfactory dissolution and bioavailability even if the tablets disintegrate over a period of many minutes, instead of immediately.

#### DETAILED DESCRIPTION OF THE INVENTION

As aforesaid, it has been found that the water-solubility of cefuroxime axetil can be enhanced by making a co-precipitate of cefuroxime axetil with a water-soluble excipient.

The term "water-soluble excipient" will be understood to mean an ingredient having no therapeutic activity and being nontoxic (and thus suitable as an excipient) that has a solubility in water of at least 1 g per 1000 g at 20°C. The solubility will preferably be at least 1 g per 100 g at 20°C, and more preferably at least 1 g per 10 g at 20°C. Suitable water-soluble excipients will include, for example, povidone, polyethylene glycols, hydroxypropyl cellulose, methylcellulose, lactose, mannitol and sorbitol.

A preferred water-soluble excipient is povidone. The amount of the water-soluble excipient used may be from about 2% to about 60% of the total weight of the co-precipitate, preferably from about 5% to about 25%, and most preferably about 10%.

The co-precipitate is made by dissolving pure crystalline cefuroxime axetil and the water-soluble excipient in a solvent or combination of solvents and evaporating the solvent or solvents. The solvent or solvents used will preferably be a solvent or solvents in which the cefuroxime axetil and the water soluble excipient have relatively high solubility so as to minimize the amount of solvent needed.

Since cefuroxime axetil has low solubility in water, it follows that a solvent other than water must be used to dissolve the cefuroxime axetil. Of the common organic solvents, the solvent in which cefuroxime axetil is most soluble is acetone. Acetone is thus a preferred solvent.

If the solvent selected to dissolve the cefuroxime axetil is also a good solvent for the water-soluble excipient, then only this one solvent is needed to dissolve both. However, if the solvent selected to dissolve the cefuroxime axetil is not a good solvent for the selected water-soluble excipient, then a second solvent is needed to dissolve the water-soluble excipient. That second solvent may be water or another organic solvent.

If two solvents are used, they should be capable of being inter-dissolved to enable formation of a clear solution of the cefuroxime axetil and the water-soluble excipient in the combination of solvents.

A solution of the cefuroxime axetil and water-soluble excipient in the solvent or solvents may be prepared either by dissolving the cefuroxime axetil and water-soluble excipient into solvents separately and then mixing the two solutions together, or by directly adding the cefuroxime axetil and water-soluble excipient to the solvent or mixture of solvents and mixing until a clear solution is formed.

After the solution of the cefuroxime axetil and water-soluble excipient in the solvent or solvents is prepared, it is necessary to then remove the solvent or solvents to obtain a dry co-precipitate.

This may be done, for example, by evaporating the solvent or solvents in a spray drying or roller drying process, or by evaporating the solvent or solvents under vacuum.

The dried co-precipitate comprising cefuroxime axetil and the water-soluble excipient will then be further processed into a tablet.

This may be done by mixing the co-precipitate with other excipients and then processing the mixed powder into tablets on a tablet press. The other excipients will preferably include both a disintegrant and a lubricant.

The disintegrant is an ingredient which absorbs water and swells to cause the tablet to disintegrate when the tablet is immersed in gastro-intestinal fluid. Preferred disintegrants are water-insoluble cross-linked polymers, including, for example, croscarmellose sodium, sodium starch glycolate, and crospovidone.

A lubricant is needed to prevent sticking of the powder to the tooling in the tableting process. Preferred lubricants are stearic acid and metallic stearates, such as magnesium stearate.

It will be understood that, as an alternative to preparing the dry co-precipitate by evaporation of solvents and then mixing the co-precipitate with other excipients in a subsequent step, the two steps may be done together. This may be done, for example, by spraying the solution of cefuroxime axetil and the water-soluble excipient onto other excipients in a fluidized bed drying system.

The invention will be further illustrated by the following examples, which are intended to be illustrative but not limiting of the scope of the invention.

#### EXAMPLE 1

2000 g of acetone and 200 g of methanol were placed in a beaker. While stirring, 500 g of pure crystalline cefuroxime axetil was slowly added, and stirring was continued for about 5 minutes, until the cefuroxime axetil was fully dissolved. Stirring was continued and 50 g of hydroxy propyl cellulose was then added. Stirring was continued for another several minutes, until the hydroxy propyl cellulose was fully dissolved. The solution was then spray-dried to obtain a co-precipitate comprising 1 part hydroxypropyl cellulose to 10 parts cefuroxime axetil.

#### EXAMPLE 2

The following were mixed together:

co-precipitate from example 1	-	134.2 g
croscarmellose sodium	-	44.0 g
magnesium stearate	-	1.0 g
colloidal silicon dioxide	-	<u>0.8 g</u>
Total	-	180.0 g
		=====

The mixed powder was compacted into slugs on a tablet press. The slugs were then ground into granules, and the granules were recompressed on a tablet press into tablets of weight 900 mg.

In view of the proportions of ingredients as aforesaid, each tablet contained 671 mg of co-precipitate, which in turn contained 610 mg of cefuroxime axetil, which in turn is equivalent to about 500 mg of cefuroxime.

The tablets were tested for disintegration time using the method set out in the United States Pharmacopoeia, 23rd edition, page 1791. The disintegration time was over 30 minutes.

The tablets were also tested for dissolution as set out in the United States Pharmacopoeia, 23rd edition, page 316. The result was about 65% in 20 minutes and 90% in 60 minutes.

The dissolution specifications for cefuroxime axetil tablets on the said page 316 are 65% in 20 minutes and 80% in 60 minutes. The tablets of this example were thus found to comply with this specification, despite the relatively slow disintegration.

The dissolution specifications in the United States Pharmacopoeia are designed to ensure that tablets meeting the specifications will exhibit acceptable bioavailability.

### EXAMPLE 3

2000 g of acetone and 200 g of methanol were placed in a beaker. While stirring, 500 g of pure crystalline cefuroxime axetil was slowly added, and stirring was continued for about 5 minutes, until the cefuroxime axetil was fully dissolved. Stirring was continued and 50 g of povidone was then added. Stirring

was continued for another several minutes, until the povidone was fully dissolved. The solution was then spray-dried to obtain a co-precipitate comprising 1 part povidone to 10 parts cefuroxime axetil.

5

#### EXAMPLE 4

The following were mixed together:

10	co-precipitate from example 3	-	132.0 g
	croscarmellose sodium	-	43.6 g
	magnesium stearate	-	1.0 g
	colloidal silicon dioxide	-	<u>0.8 g</u>
	Total	-	177.4 g
15			=====

The mixed powder was compacted into slugs on a tablet press. The slugs were then ground into granules, and the granules were recompressed on a tablet press into tablets of weight 900 mg.

20

Again, in view of the proportions of ingredients as aforesaid, each tablet contained 670 mg of co-precipitate, which in turn contained 609 mg of cefuroxime axetil, which in turn is equivalent to about 500 mg of cefuroxime.

25

The tablets were tested for disintegration time using the method set out in the United States Pharmacopoeia, 23rd edition, page 1791. The disintegration time was about 10 minutes.

30

The tablets were also tested for dissolution as set out in the United States Pharmacopoeia, 23rd edition, page 316. The result was over 80% in 20 minutes and over 90% in 60 minutes.

The tablets of this example thus exhibited dissolution substantially faster than required by the United States Pharmacopoeia, again despite the fact that disintegration was not immediate.

5

10

15

20

25

30

What is claimed is:

1. A co-precipitate comprising cefuroxime axetil and a water-soluble excipient.
2. A co-precipitate as in claim 1 comprising from about 40% to about 98% by weight cefuroxime axetil and from about 2% to about 60% by weight water-soluble excipient.
3. A co-precipitate as in claim 1 comprising from about 75% to about 95% by weight cefuroxime axetil and from about 5% to about 25% by weight water-soluble excipient.
4. A co-precipitate as in claim 1 comprising about 90% by weight cefuroxime axetil and about 10% by weight water-soluble excipient.
5. A co-precipitate as in any of claims 1 to 4 wherein the water-soluble excipient is selected from the group consisting of povidone, hydroxy propyl cellulose, methycellulose, lactose, mannitol and sorbitol.
6. A process of production of a co-precipitate of any of claims 1 to 5 which comprises:-
  - dissolving the cefuroxime axetil and water-soluble excipient in a solvent or a mixture of solvents; and
  - evaporating the solvent or solvents.
7. A process as in claim 6 wherein acetone is used as solvent.
8. A process as in claim 6 wherein the solvent or solvents are evaporated by spray-drying.

9. A pharmaceutical tablet comprising a co-precipitate according to any of claims 1 to 5.

- 5 10. A pharmaceutical tablet as in claim 9 further comprising a disintegrant.

11. A pharmaceutical tablet as in claim 10 wherein the disintegrant is a water-insoluble cross-linked polymer.

- 10 12. A pharmaceutical tablet as in claim 10 wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.

13. A pharmaceutical tablet as in claim 10 further comprising a lubricant.

- 15 14. A pharmaceutical tablet as in claim 13 wherein the lubricant is stearic acid or a metallic stearate.

ABSTRACT

5

A co-precipitate of cefuroxime axetil and a water-soluble excipient. Process for making said co-precipitate, and pharmaceutical compositions for oral administration comprising said co-precipitate.

10

15

20

25

30

**RULE 63 (37 C.F.R. 1.63)**  
**DECLARATION AND POWER OF ATTORNEY**  
**FOR PATENT APPLICATION**  
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**PHARMACEUTICAL COMPOSITIONS COMPRISING CEFUROXIME AXETIL**

the specification of which (check applicable box(es):

- ☒ Is attached hereto  
☐ Was filed on \_\_\_\_\_ as U.S. Application Serial No. \_\_\_\_\_ (Atty Dkt. No. \_\_\_\_\_)  
☒ Was filed as PCT international application No. PCT/CA98/00773 on AUGUST 7, 1998  
 And (if applicable to U.S. or PCT application) was amended on \_\_\_\_\_

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application.

**Prior Foreign Application(s):**

**Application Number**  
**2,209,868**

**Country**  
**CANADA**

**Day/Month/Year Filed**  
**15 AUGUST, 1997**

I hereby claim the benefit under 35 U.S.C. §119(e) if any United States provisional application(s) listed below.

**Application Number** **Day/Month/Year Filed**

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application:

**Prior U.S./PCT Application(s):**

**Application Serial No.**  
**PCT/CA98/00773**

**Day/Month/Year Filed**  
**7 AUGUST, 1998**

**Status: patented, pending,  
 abandoned**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. I hereby appoint **NIXON & VANDERHYE, P.C., 1100 North Giebe Rd., 8<sup>th</sup> Floor, Arlington, VA 22201-4714, telephone number (704) 816-4000** (to whom all communications are to be directed), and the following attorneys thereof (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076; James T. Hosmer, 30184; Robert W. Faris, 31352; Richard G. Besha, 22770; Mark E. Nesbaum, 32348; Michael J. Keenan, 32108; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Paul J. Henon, 33626; Jeffrey H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr., 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Jerry D. Craig, 38026; Alan M. Kagen, 36178; William J. Griffin, 31280.

1. Inventor's Signature: BERNARD CHARLES SHERMAN Date FEB 10, 2000 CANADIAN  
 Inventor (first) MI (last) (citizenship)  
 Residence: (city) WILLOWDALE (state/country) ONTARIO, CANADA  
 Post Office Address: 50 OLD COLONY ROAD  
 (zip code) M2L 2K1

FOR ADDITIONAL INVENTORS, Check box ☐ and attach sheet with same information and signature and date for each

A: uspatent/attor